EXHIBIT B

^{13}C Nuclear Magnetic Resonance Studies on the Conformation of Substituted Hydantoins [1]

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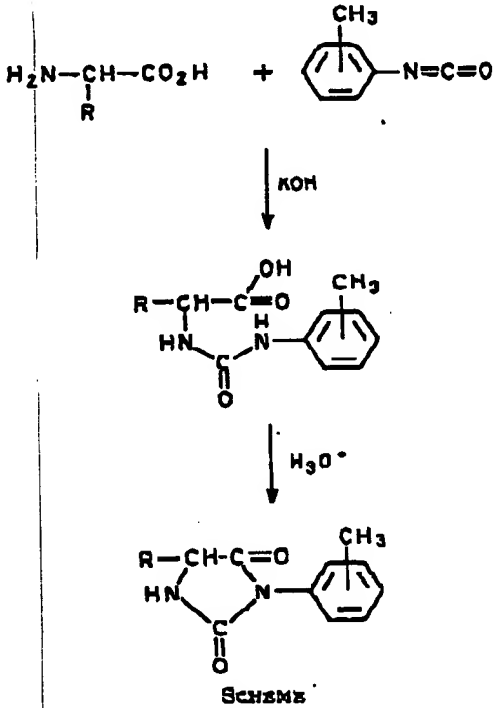
A number of hydantoins were synthesized and their ^{13}C n.m.r. spectra were studied using special solvents and shift reagents. Some interesting features of their conformation were deduced. In the case of hydantoins derived from phenylalanine evidence was found for non-bonded attraction between the hydantoin ring and the phenyl group in the side chain.

In recent years ^1H n.m.r. spectroscopy has been shown to be a valuable tool for studies on conformation. The advent of Fourier transform accessories for ^{13}C n.m.r. spectroscopy has now provided an additional physical organic method for conformation determination. In general, chemical shifts from ^{13}C n.m.r. spectra are more responsive than those in ^1H n.m.r. spectra to changes in stereochemistry and are therefore more informative about conformation. We present here an account of the synthesis of a number of hydantoins and a study of their ^{13}C n.m.r. spectra using various techniques including some reported recently from our laboratory.[2,3]

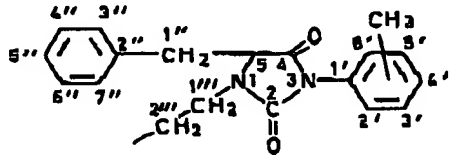
Some of the hydantoins under study were prepared from amino acids and an appropriate isocyanate (see Scheme). Two thiohydantoins (2c and e) were prepared by using isothiocyanates.

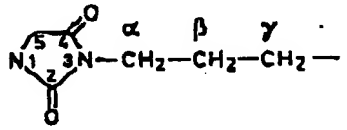


Scheme

For *N*-alkylation leading to 1-substitution in hydantoins, we found it convenient to conduct the alkylation in hexamethylphosphoramide (HMPA) solution using sodium hydride as a base.

^{13}C *N.m.r. Spectral Assignments.*—For convenience in comparing spectral data the following uniform numbering system has been used. Variously substituted hydantoins and thiohydantoins studied during the

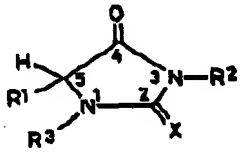




course of this investigation are listed in Table 1. The ^{13}C chemical shifts of most of these compounds are presented in Tables 2—5. Tables 6—8 show a comparison between the ^{13}C chemical shifts of hydantoins (2d), (3b),

TABLE 1

Hydantoins used in n.m.r. analysis



Compound	X	R^1	R^2	R^3
(1a)	O	H	H	H
(1b)	S	H	C_6H_5	H
(1c)	O	CH_3	C_6H_5	CH_3
(2a)	O	$C_6H_5CH_2$	H	H
(2b)	O	$C_6H_5CH_2$	CH_3	H
(2c)	S	$C_6H_5CH_2$	CH_2CH_3	H
(2d)	O	$C_6H_5CH_2$	$CH_2CH_2CH_3$	H
(2e)	S	Indol-3-ylmethyl	CH_2CH_3	H
(3a)	O	H	C_6H_5-*o*-CH_3	H
(3b)	O	CH_3	C_6H_5-*o*-CH_3	H
(3c)	O	$CH_3(CH_2)CH$	C_6H_5-*o*-CH_3	H
(3d)	O	$CH_3CH_2(CH_3)CH$	C_6H_5-*o*-CH_3	H
(3e)	O	C_6H_5	C_6H_5-*o*-CH_3	H
(3f)	O	$C_6H_5CH_2$	C_6H_5-*o*-CH_3	H
(3g)	O	$C_6H_4(p)(Cl)CH_2$	C_6H_5-*o*-CH_3	H
(3h)	O	Indol-3-ylmethyl	C_6H_5-*o*-CH_3	H
(3i)	O	$C_6H_5CH_2$	C_6H_5-*o*-CH_3	CH_3
(3j)	O	H	C_6H_5-*o*-CH_3	$C_6H_5CH_2CH_2$
(4a)	O	H	C_6H_5-*m*-CH_3	H
(4b)	O	$C_6H_5CH_2$	C_6H_5-*m*-CH_3	H
(5a)	O	H	C_6H_5-*p*-CH_3	H
(5b)	O	$C_6H_5CH_2$	C_6H_5-*p*-CH_3	H

and (3f) before and after addition of $Eu(fod)_3$ and $TiCl_4$ (Tables 7 and 8). Table 9 is a comparison between the estimated and observed chemical shifts of the 3-arylhydantoins (3a)—(5a). The effect of $Eu(fod)_3$ on the ^{13}C chemical shifts of the hydantoin (4a) is listed in Table 10.

TABLE 2

Carbon-13 chemical shifts (p.p.m.) of hydantoins (1a—c)

Carbon	(1a)	(1b)	(1c)
C-2	161.74	156.66	155.16
C-4	174.37	171.21	172.12
C-5	47.80	45.96	56.97
C-1′		132.60	132.18
C-2′		126.53	126.03
C-3′		128.82	128.34
C-4′		127.74	127.86
C-5′		128.82	128.94
C-6′		126.56	126.03
C-1″			15.21
C-1‴			27.82

Most of the hydantoins were soluble in chloroform but there were a few that had such low solubility in that solvent that recording their ^{13}C n.m.r. spectra proved to be a problem. Recently we reported our observation that arsenic trichloride is a convenient solvent for ^{13}C n.m.r. measurements.[3] We also showed that the chemical shift of a carbon carrying an amino- or hydroxy-group and its immediate neighbour is affected by $AsCl_3$ but for other carbons the chemical shift in chloroform and $AsCl_3$ are nearly identical.* Shift reagents such as $Eu(fod)_3$ and $TiCl_4$ were found to be compatible with $AsCl_3$ as solvent. In the present study we have used a mixture of $AsCl_3$ and $CDCl_3$ (to provide a ^2H signal for the internal lock) for hydantoins of low solubility in $CDCl_3$.

Spectral Assignments.—The ^{13}C n.m.r. spectrum of unsubstituted hydantoin (1a) showed the two carbonyl resonances (C-2 and -4) at δ 161.74 and 174.37 p.p.m. In substituted hydantoins these carbonyl carbon peaks

TABLE 3

Carbon-13 chemical shifts (p.p.m.) of hydantoins (2a—c and e)

Carbon	(2a)	(2b)	(2c)	(2c) *
C-2	156.45	157.86	169.97	
C-4	175.01	173.61	173.18	174.79
C-5	56.37	55.59	60.42	60.53
C_α		24.39	36.15	35.93
C_β			18.62	18.80
C_γ				
C-1″	36.47	37.67	37.33	27.40
C-2″	135.74	135.52	134.55	
C-3″	129.70	129.50	129.37	
C-4″	128.08	128.72	128.83	
C-5″	126.57	127.32	127.54	
C-6″	128.80	128.72	128.83	
C-7″	129.70	129.59	129.37	

* The chemical shifts of the indole carbons are as follows: 108.43, 111.89, 119.33, 119.64, 122.14, 124.84, 128.20, and 137.00 p.p.m.

were found in the δ 156—162 and 171—174 p.p.m. ranges. A distinction between C-2 and -4 was made from a comparison of the spectra for (2b) (Table 3) and (2d) (Table 6) and their thiohydantoin analogue (2c) (Table 3). In (2c) the lowest field carbon resonances appear at δ 153.4 and 173.2 p.p.m.: obviously the C-2 resonance is shifted upfield by *ca.* 4 p.p.m. on replacing oxygen with sulphur but the C-4 resonance is hardly affected as is to be expected. The C-4 resonance is

TABLE 4

Carbon-13 chemical shifts (p.p.m.) of hydantoins (3a, c—e, and g—j) from *o*-tolyl isocyanate

Carbon	(3a)	(3c)
C-2	157.86	157.52
C-4	170.48	172.73
C-5	45.72	62.47, 62.90
C-1′	130.34	130.76
C-2′	128.51	128.39, 128.71
C-3′	129.59	129.36
C-4′	126.69	126.88
C-5′	131.21	131.19
C-6′	136.39	136.27, 136.59
o-CH_3	17.70	17.80, 18.02

Carbon	(3d)	(3e) *	(3g)
C-2	157.52	155.92	156.46
C-4	173.06	170.37	172.00
C-5	61.17, 61.61	60.31, 60.42	58.16, 58.37
C-1′	129.78	130.88	130.56
C-2′	128.39, 128.71	128.40	128.19, 128.51
C-3′	129.36	129.59	129.89
C-4′	126.78	126.40	126.89
C-5′	131.19	130.88	131.53
C-6′	136.37, 136.59	136.06, 136.39	136.49
o-Me	17.69, 18.02	17.07, 17.24	16.83, 17.70
C-1″			36.56, 36.90
C-2″		127.97	133.80
C-3″		128.72	131.31, 131.53
C-4″		126.02	128.94
C-5″		133.15	131.16
C-6″		126.02	126.94
C-7″		128.72	131.31, 131.53
C-8″			
C-9″			

	(3h) †	(3i)	(3j)
C-2	155.81	155.80	155.48
C-4	172.21	170.81	168.64
C-5	57.10, 57.62	62.26, 62.60	44.13
C-1′	130.77	129.80	130.88
C-2′	127.97, 128.51	127.65, 129.97	128.72
C-3′	129.59	129.16	129.37
C-4′	126.46	126.46	126.78
C-5′	130.77	131.00	131.10
C-6′	136.39	136.32, 136.60	136.28
o-Me	15.97, 17.26	16.72, 17.70	17.70
C-1″	26.76, 27.08	34.53, 34.96	50.18
C-2″		134.44	34.10
C-3″		120.02	138.11
C-4″		126.62	126.72
C-5″		127.43	128.72
C-6″		128.62	126.78
C-7″		130.02	128.72
C-8″			126.72
C-9″			
C-1‴ (1-Me)		28.27, 28.59	

† In $CDCl_3$–$AsCl_3$. The chemical shifts of the indole carbons are as follows: 107.68, 111.35, 118.47, 119.86, 122.14, 123.55, 120.59, and 135.41 p.p.m.

modified slightly on substitution at C-5. Changes at C-5 or substitution on N-1 [(1c), Table 2; (3i, j), Table 4] have little effect on the C-2 resonance.

The alkyl carbon resonances in the hydantoins under study were mostly assigned by comparison with closely

* $AsCl_3$ Solutions must be handled with due regard for their toxicity. See ref. 3 for appropriate procedures.

TABLE 5

Carbon-13 chemical shifts (p.p.m.) of hydantoins (4a and b) and (5a and b) from *m*- and *p*-tolyl isocyanate

Carbon	(4a)	(4b)	(5a) *	(5b)
C-2	157.86	156.78	157.32	158.56
C-4	170.81	172.42	171.77	173.07
C-5	46.60	58.05	46.60	58.37
C-1′	131.76	131.64	130.27	129.37
C-2′	123.64	123.44	127.00	127.64
C-3′	128.94	128.83	129.70	129.80
C-4′	129.26	129.16	138.00	138.21
C-5′	139.30	139.08	129.70	129.80
C-6′	127.11	127.11	127.00	127.64
Ar-Me	21.26	21.26	21.04	21.04
C-1″		37.77		37.98
C-2″		134.88		136.16
C-3″, C-7″		130.80		130.66
C-4″, C-6″		128.62		128.94
C-5″		127.32		128.60

* In [$^2H_6$]DMSO.

related hydantoins. Additional information was provided by off-resonance decoupling which easily distinguished between primary, secondary, and tertiary carbon signals. The signals due to benzyl and indol-3-ylmethyl moieties were recognized by comparison with

TABLE 6

^{13}C N.m.r. spectra of 5-benzyl-3-propylhydantoin (2d) [δ (p.p.m.)]

Carbon	$CDCl_3$ Solution	$Eu(fod)_3$ added
C-2	157.97	158.83
C-4	173.50	173.60
C-5	58.27	58.81
C-1′	40.25	40.79
C-2′	21.26	21.58
C-3′	11.11	11.32
C-1″	37.77	38.09
C-2″	135.20	135.41
C-3″, C-7″	129.59	129.80
C-4″, C-6″	128.72	128.93
C-5″	127.32	127.43

the spectra of appropriate amino-acids[4] and cyclic peptides.[5]

The spectral assignment for aromatic carbons in 3-arylhydantoins was made from a comparison with data on acetanilide and toluene.[6] In 3-phenylhydantoins (1b and c) (Table 2), C-1′ and -4′ peaks were differentiated from the peaks of (C-2′ + C-6′) and (C-3′ + C-5′) by

TABLE 7

^{13}C N.m.r. spectra of 5-methyl-3-*o*-tolylhydantoin (3b) [δ (p.p.m.)]

Carbon	$CDCl_3$ Solution	$Eu(fod)_3$ added	$TiCl_4$ added
C-2	156.78	157.75, 157.36	159.16
C-4	173.85	173.72	173.96
C-5	53.19	53.51, 53.92	54.17, 54.38
C-1′	130.07	131.15	131.73
C-2′	136.39, 136.60	136.83, 139.05	136.62
C-3′	129.80	126.89	127.00
C-4′	126.78	129.70	129.92
C-5′	131.10	131.31	131.21
C-6′	136.38, 136.49	136.82	136.60
o-Me	17.69, 17.91	17.70, 17.91	17.48, 17.80
C-1″	17.48	18.13	17.05

TABLE 8

^{13}C N.m.r. spectra of 5-benzyl-3-*o*-tolylhydantoin (3f) [δ (p.p.m.)]

Carbon	$CDCl_3$ solution	$Eu(fod)_3$ added	$TiCl_4$ added
C-2	156.67	158.18, 158.62	158.15, 158.51
C-4	172.21	172.53	171.60, 171.78
C-5	58.16, 58.48	58.91, 58.24	58.91, 59.24
C-1′	130.45	131.41	131.75
C-2″	136.19, 136.50	136.73	136.08, 136.72
C-3′	129.37	129.59	129.48, 129.70
C-4′	126.67	127.00	126.67
C-5′	131.10	131.21	131.10
C-6′	136.30, 136.60	136.93, 137.14	136.60
o-Me	16.83, 17.59	17.37, 17.91	16.51, 16.94
C-1″	37.11, 37.44	37.65, 37.87	36.58, 36.90
C-2″	134.66	134.98	133.90
C-3″, C-7″	129.92, 130.45	130.34	130.24
C-4″, C-6″	128.51	128.73	128.72
C-5″	127.32	127.54	127.43

consideration of the relative intensity of the peaks. This approach could not be used for 3-tolylhydantoins because of lack of symmetry. Of the two peaks corresponding to C-1′ and -4′ the one at lower field has to

TABLE 9

o-Tolylhydantoin (3a)

Substituent effect (p.p.m.)

	CH_3	Hydantoin	Estimated	Observed	Δ*
C-6	+0.6	+4.5	133.3	130.3	−3.0
C-7	−0.2	2.8	126.4	128.5	+2.1
C-8	−3.1	−3.0	125.7	126.9	+1.2
C-9	−0.2	−1.2	117.5	129.6	+2.1
C-10	+0.6	0.7	129.4	131.21	+1.8
C-11	+9.1	+7.0	135.7	136.4	+0.7
		m-Tolylhydantoin (4a)			
C-6	−0.2	+3.9	132.4	131.8	−0.6
C-7	−3.1	−2.1	123.5	123.5	0
C-8	−0.2	+0.1	126.6	129.3	+0.7
C-9	0.6	−1.0	128.3	128.9	+0.6
C-10	9.1	+0.1	137.9	139.3	+1.4
C-11	+0.6	−2.1	127.2	127.1	0
		p-Tolylhydantoin (5a)			
C-6	−3.1	+3.9	129.6	130.3	0.7
C-7	−0.2	−2.1	126.4	127.0	0.3
C-8	+0.6	+0.1	129.4	129.7	0.3
C-9	+9.1	−1.0	136.8	138.0	1.2
C-10	−0.6	+0.1	129.4	129.7	0.3
C-11	+0.2	−2.1	126.4	127.0	0.3

* $\Delta = \delta_{obs} - \delta_{est}$

correspond to C-1′ because of substitution on that carbon.

In case of the 3-tolylhydantoins each aromatic carbon displays a separate peak. Substituent effects at the α, β, and γ positions were deduced for the hydantoin moiety from the spectrum of (1b) (Table 2); similar substituent effects were also deduced for methyl sub-

TABLE 10

Effect of $Eu(fod)_3$ on the chemical shift (p.p.m.) of *m*-tolylhydantoin (4a)

Carbon	Chemical shift	+$Eu(fod)_3$	Δ
C-6	131.76	132.32	1.18
C-7	123.54	124.62	1.18
C-8	129.26	129.80	0.54
C-9	128.94	129.48	0.54
C-10	139.30	139.72	0.42
C-11	127.11	128.08	0.97
C-12	21.26	21.47	0.22

stitution in toluene. Assuming additivity, the chemical shift of aromatic carbons in (3a)—(5a) were estimated. For the *m*- and *p*-tolyl substituents in (4a) and (5a) the observed chemical shifts were in fairly good agreement (Table 9). In case of (3a) (Table 9), however, the agreement was quite poor. This difference is due to the restricted rotation of the aromatic ring along its axis when an *o*-methyl group is present. The *m*- and *p*-methyl substituent in (4a) and (5a) do not interfere with the free rotation of the aromatic ring.

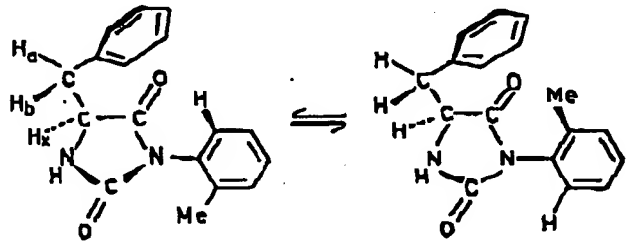
The restricted rotation of the aromatic ring in (3a) leads to two rotamers: in one, the *o*-methyl group is above the plane of the hydantoin ring, in the other, the *o*-methyl group is below that plane. The observed non-equivalence is not due to nitrogen-inversion at N-1 and -3 since the hydantoin ring was shown to be planar in two hydantoins whose *X*-ray structures were determined.[8] Models show that coplanar *o*-tolyl and hydantoin rings would be sterically hindered and so this possibility for explaining the non-equivalence of the *o*-methyl groups is unlikely.

Conformation of Hydantoins.—Introduction of a substituent at C-5 in 3-*o*-tolylhydantoin leads to loss of symmetry and two distinct rotamers now become possible. In one the *o*-methyl group is *cis* to the 5-substituent, in the other it is *trans*. As long as the interconversion of these two rotamers is slow on the n.m.r. time scale, two sets of peaks should be displayed by the hydantoin in its n.m.r. spectrum. Previously we have noted that ^{1}H n.m.r. is not sensitive enough to record the difference between these rotamers.[1] Because of higher sensitivity of ^{13}C n.m.r. there are perceptible differences between the spectra of the two rotamers in a number of cases (Tables 4, 7, and 8). The hydantoins (3a and j) (Table 4) have a plane of symmetry if the five-membered heterocycle ring is considered to be planar on the n.m.r. time scale; these two compounds, therefore, show only one set of peaks for the various carbons. The hydantoins (3b—i) (Tables 4 and 7), all display doublet peaks for the *ortho*-carbons (2′ and 6′) and the *o*-methyl carbon. All these compounds excepting (3b) also show that the spectral difference between two rotamers can be enhanced by the use of n.m.r. shift reagents. Thus, the addition of Eu(fod)$_3$ to a chloroform solution of (3b) converted the C-2 and -5 singlets into doublets; on the other hand, C-6′, which carries an *o*-Me group, was reduced to a singlet from a doublet. In the case of (3f), Eu(fod)$_3$ resolved the C-2 singlet into a doublet. The europium reagent must co-ordinate preferentially with the NH–CO group because the other carbonyl carbon (C-4) is unaffected by the addition of Eu(fod)$_3$.

Recently we have shown that titanium tetrachloride serves as a useful shift reagent for studying the ^{13}C n.m.r. spectra of carbonyl compounds.[2] When this reagent was added to (3b), C-5 was resolved into a doublet separated by 0.2 p.p.m., the C-1′ and *o*-Me peaks also became doublets, the C-2 peak was shifted downfield by 2.4 p.p.m., but the C-4 resonance was unchanged. Obviously, titanium tetrachloride is co-ordinated with the NH–CO group but there is little interaction with the other oxo-group.

Non-bonded Interactions.—On the basis of ^{1}H n.m.r. and *X*-ray diffraction evidence we have shown that hydantoin derivatives of phenylalanine in solution and the solid state prefer a folded conformation.[1,6] In all probability, there is a strong dipole–dipole interaction between the hydantoin and the π-electrons of the benzyl group at C-5 which leads to attraction between the two groups. This attraction obviously more than compensates for the steric repulsion due to crowding.

The *o*-Me group in conformation (3f) (Figure) is apparently far enough away from the phenyl ring of the



(3f) (3f′)

Conformations (3f and f′)

C-5 substituent because one of the peaks for the *o*-methyl group appears at *ca.* 170 p.p.m. in the spectra of (3a—j), the other *o*-methyl signal corresponding to the conformation (3f′) shifts from compound to compound. The separation between these two methyl peaks increases when an alkyl substituent at C-5 is replaced by a phenyl group (3e) (Table 4) and then by a benzyl group (3f) (Table 8). Substitution of a indol-3-ylmethyl group (3h) (Table 4) produces an even more noticeable upfield shift.

The folded conformation observed by *X*-ray crystallography for compound (3g) is thus a common feature for compounds (3f, h, and i) based on the ^{13}C n.m.r. data reported here.

We have reported previously that the ^{1}H n.m.r. data indicate folded conformation for (2b—e); the protons of the alkyl side chain at N-3 are shifted considerably upfield under the influence of the ring current of the phenyl ring of the 5-benzyl group. The effect of this ring current on C-13 chemical shifts must diminish rapidly with distance because the C-2′ and -6′ resonances or the Me resonance in (4b) and (5b) are not much shielded by the phenyl ring on the side chain at C-5. The indol-3-ylmethyl group is more effective than the phenyl group in producing upfield shifts for the aliphatic side chain at N-3 [see (2c) *versus* (2e) in Table 3].

Conclusions.—The present study shows that the ^{13}C n.m.r. spectra provide a convenient probe for details of conformation of substituted hydantoins. As is to be expected, ^{13}C n.m.r. spectra are far more sensitive than ^{1}H n.m.r. spectra to stereochemical features, for example, lack of symmetry as in alanylhydantoin (1c) *versus* glycylhydantoin (1a).

Our *X*-ray diffraction studies[8] had revealed that in

p-chlorophenylalanylhydantoin, the phenyl group of the benzyl side chain was folded over the hydantoin ring. This crowded conformation could have been due to some special feature of the crystal lattice of this hydantoin. The ^{13}C n.m.r. spectra of phenylalanylhydantoins, however, showed preference for the same crowded conformation in chloroform solution. In addition $J_{H^{\alpha}H^{\beta}}$ coupling constants [9] in the $CH_2(1'')$–$CH(5)$ fragment indicate a folded conformation. Thus the crowded conformation might be preferred because of non-bonded attraction between the aryl group of the side-chain and the dipole of the hydantoin ring system and not because of special constraints inherent in the crystal structure of *p*-chlorophenylalanylhydantoin.

The indole group in the side chain of tryptophanylhydantoins exerted more influence on the chemical shift of the 3-substituents than the phenyl group in the side chain of the phenylalanylhydantoin (3f).

On the basis of the ^{13}C n.m.r. studies reported here and our previous ^1H n.m.r. studies, it is quite evident that in solutions of peptides and proteins containing aromatic amino-acids, special conformational preferences exist that are not present in peptides containing only aliphatic amino-acids. These special conformational features in proteins containing tryptophan, phenylalanine, and other aromatic amino-acids are likely to influence binding of these proteins to receptors and their structure–activity relationship.

EXPERIMENTAL

^{13}C N.m.r. spectra were recorded by pulse Fourier transform on a Bruker HX-90 spectrometer employing an external ^{19}F for an internal ^2H lock and broad-band proton decoupling (90 MHz); an operating frequency of 22.636 MHz was used for the ^{13}C nucleus and Me_4Si was used as internal reference; ^{13}C chemical shifts are δ values relative to Me_4Si.

For studying the effect of n.m.r. shift reagents a $CDCl_3$ solution of the hydantoin (150—200 mg) and Me_4Si was placed in a 10 mm o.d. n.m.r. tube. Several drops of titanium tetrachloride or *ca.* 75 mg of $Eu(fod)_3$ were added to this solution. After shaking for 1 or 2 min a clear solution was obtained which was used for recording ^{13}C n.m.r. spectra.

Mass spectral measurements were made on a Hitachi-Perkin-Elmer RMU-7 spectrometer at an ionizing potential of 70 eV. Samples were introduced through a direct probe. I.r. spectra were recorded as Nujol mulls on a Hitachi-Perkin-Elmer model 247 grating spectrometer. Elemental analyses were performed by Alfred Bernhardt, Max Planck Institute, Mülheim, W. Germany. M.p.s were determined in open capillary tubes and are uncorrected. Amino-acids, isocyanates, and HMPA were obtained from Aldrich.

Preparation and Spectral Properties of Hydantoins.—The hydantoin (1a) was purchased from Aldrich, and used for n.m.r. studies without further purification. A number of hydantoins were prepared from the appropriate amino-acid and isocyanate using the method of Finkbeiner.[10] The preparation of the following hydantoins has been previously described by us: [1] (2a—d), (3a—c), (3e—h), (4a, b), and (5a and b).

1,5-*Dimethyl*-3-*phenylhydantoin* (1c).—3-Phenylhydantoin [10] (1b) (5.6 g, 0.032 mol) was added to an ice-cold solution of sodium hydride (1.0 g, 0.04 mol) in HMPA (30 ml). The mixture became coloured as hydrogen was evolved. After stirring overnight at room temperature the colour was dark violet. Methyl iodide (8.0 g, 0.056 mol) was added slowly to the mixture which was then stored for 5 h at room temperature. Water (100 ml) was added to terminate the reaction and after some time the aqueous layer was separated and cooled in a refrigerator. The desired product, 1,5-dimethyl-3-phenylhydantoin (1c), was obtained in 65% yield, m.p. 100 °C (lit.,[10] 100—110 °C); *m/e* 190 (M^+); $\nu_{max.}$ (Nujol) 1 701 cm^{-1} (CONR).

5-*Benzyl*-1-*methyl*-3-*o*-*tolylhydantoin* (3i).—Using the procedure described for (1c) above, (3f) was methylated in 72% yield to give (3i), $\nu_{max.}$ (Nujol) 1 698 cm^{-1} (CON); δ ($CDCl_3$) 1.48 (1.8 H, s, 3/5 of OCH_3), 2.19 (1.2 H, s, 2/5 of OCH_3), 3.09 (3 H, s, CH_3N), 3.26 (2 H, d, *J* 5.0 Hz, $PhCH_2$), 4.3 (1 H, t, *J* 5.0 Hz, CHCO), 6.28 (0.4 H, d, 7.0 Hz, 2/5 of OH), 7.05—7.45 (3.6 H, m, aromatic), and 7.24 (5 H, s); *m/e* 294 (M^+).

1-*Phenethyl*-3-*o*-*tolylhydantoin* (3j).—This *compound*, m.p. 87—88°, was prepared in 65% yield by the alkylation of (1a) with phenethyl bromide. $\nu_{max.}$ (Nujol) 1 701 cm^{-1} (CON); δ ($CDCl_3$) 2.14 (3 H, s, OCH_3), 2.83 (2 H, m, $PhCH_2$), 3.70 (2 H, m, CH_2N), 3.80 (2 H, s, CH_2C), and 6.90—7.30 (10 H, m, aromatic); *m/e* 194 (M^+) (Found: C, 73.65; H, 5.8; N, 9.4. $C_{16}H_{16}N_2O_2$ requires C, 73.4; H, 6.15; N, 9.55%).

5-*Benzylhydantoin* (2a).[7]—This compound had $\nu_{max.}$ (Nujol) 1 694 cm^{-1} (CONH); δ ([$^2H_6$]DMSO) 2.97 (2 H, d, *J* 5.0 Hz, $PhCH_2$), 4.33 (1 H, t, *J* 5.0 Hz, $COCH_2$), 7.22 (5 H, s, C_6H_5), and 7.84br (2 H).

5-*Benzyl*-3-*methylhydantoin* (2b).—This compound was prepared by the methylation of (2a) as described for (1c), m.p. 125—130°, $\nu_{max.}$ (Nujol) 1 694 cm^{-1} (CONH); δ ($CDCl_3$) 2.84 (1 H, q, ABX pattern, *J* 8.0 Hz, H_A of CH_2), 3.31 (1 H, q, ABX pattern, *J* 8.0 Hz, H_B of CH_2), 4.23 (1 H, q, ABX pattern, H_X of CH), 0.10br (1 H, NH), and 7.25 (5 H, s, 5 H, aromatic); *m/e* 204 (M^+).

3-*Ethyl*-5-(*indol*-3-*ylmethyl*)*thiohydantoin* (2e).—This thiohydantoin was prepared in 37% yield from tryptophan and ethyl isothiocyanate following the method of Finkbeiner,[10] m.p. 162—163°; $\nu_{max.}$ (Nujol) 1 724 cm^{-1} (CSNH); δ ($CDCl_3$) 1.0 (3 H, t, *J* 8 Hz, CH_3), 3.01 (1 H, q, ABX pattern, *J* 8 Hz, H_A of CH_2), 3.45 (1 H, q, ABX pattern, *J* 4 Hz, H_B of CH_2), 3.75 (2 H, q, *J* 8 Hz, CH_2), 4.29 (1 H, q, ABX pattern, *J* 4 Hz, H_X), and 6.8—7.8 (7 H, m, indole protons).

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